[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

THE ORIENTATION IN THE NITRATION OF 3,4- AND 2,5-DIMETHYLACETOPHENONE

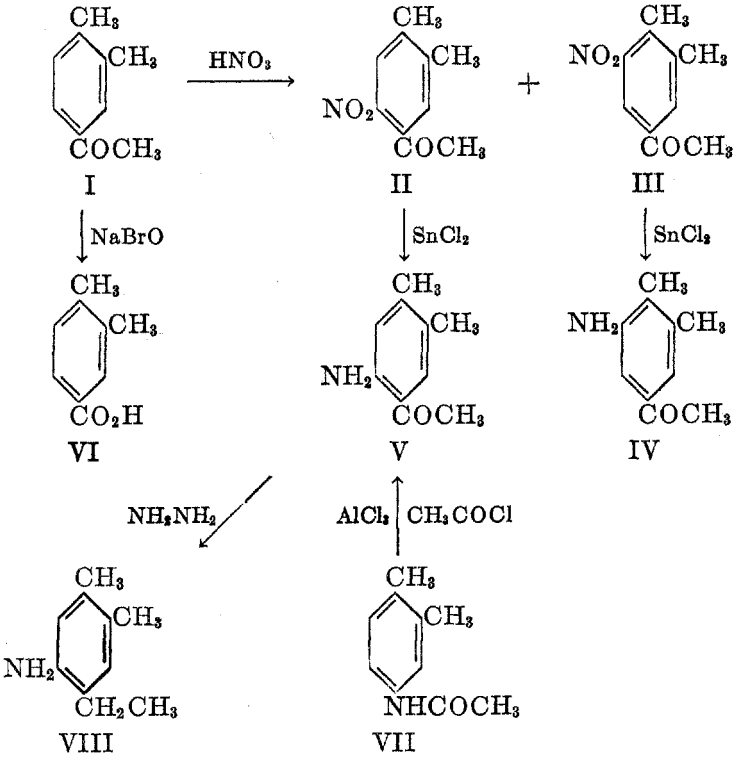
NG. PH. BUU-HOÏ, BERNARD ECKERT, AND RENÉ ROYER

Received March 10, 1952

It has recently been found (1) that a convenient route to nuclear alkylated anilines of proven constitution lies in the following sequence of reactions: (a) nitration of the appropriate homolog of acetophenone; (b) conversion of the nitro derivatives obtained to amino ketones; (c) further reduction of the ketones with the Kishner-Wolff—Huang-Minlon procedure.

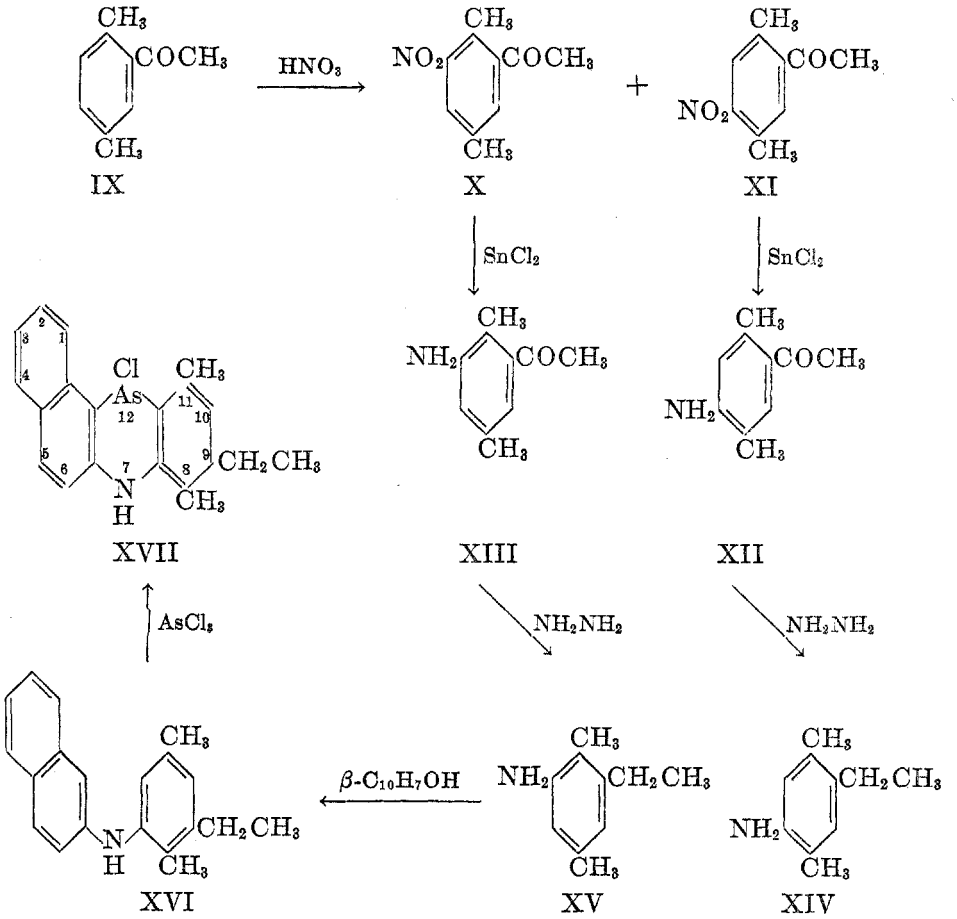
This method has now been applied to 3,4- and 2,5-dimethylacetophenone for the synthesis of some nuclear ethylxylidines which were needed in a pure condition for another research.

Acetophenone is known to be preferentially nitrated in the *meta* position under the usual experimental conditions (2), and alkylbenzenes undergo nitration in the *ortho* and *para* positions. 3,4-Dimethylacetophenone (I) could therefore be



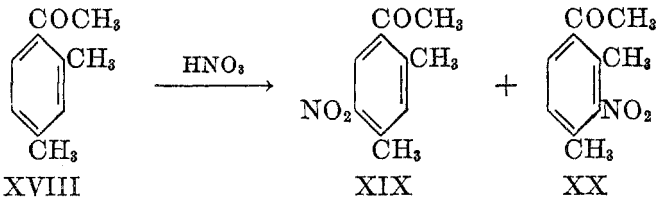
expected to give mainly 3,4-dimethyl-5-nitroacetophenone (III), but experiment showed instead that the chief nitration product was 3,4-dimethyl-6-

nitroacetophenone (II), with the *isomeric compound* (III) as *by-product*. The constitution of the former substance was determined by its reduction with stannous chloride to 6-amino-3,4-dimethylacetophenone (V). This amino ketone was prepared independently from 3,4-dimethylacetanilide (VII) and acetyl chloride by means of a Friedel-Crafts reaction (followed by N-desacetylation) (3), the acetyl radical entering the position *ortho* to the amino group. The orientation was shown by reduction of the diazo compound derived from the amine with hypophosphorous acid to 3,4-dimethylacetophenone, whose constitution was proved by sodium hypobromite oxidation to 3,4-dimethylbenzoic acid (VI); further, the Kishner-Wolff—Huang-Minlon reduction of 6-amino-3,4-dimethylacetophenone was shown to yield the already known 6-ethyl-3,4-dimethylaniline (VIII). The presence of 3,4-dimethyl-5-nitroacetophenone in the crude nitration product of 3,4-dimethylacetophenone was shown by the reduction of the mother-liquors from the crystallization of II to 5-amino-3,4-dimethylacetophenone (IV), a substance already prepared in another way (3).



In the case of 2,5-dimethylacetophenone (IX), the nitration gave a mixture of the two expected monosubstitution products: 2,5-dimethyl-3-nitro- (X) and 2,5-dimethyl-4-nitro-acetophenone (XI). These two nitro compounds were not separated, but the reduction product could be resolved into the already-known (3) well-crystallized 4-amino-2,5-dimethylacetophenone (XII), and the oily 3-amino-2,5-dimethylacetophenone (XIII). 4-Amino-2,5-dimethylacetophenone was readily reduced to 4-ethyl-2,5-dimethylaniline (XIV), already prepared in another way (4); 3-amino-2,5-dimethylacetophenone was similarly reduced to 3-ethyl-2,5-dimethylaniline (XV); the constitution of this base was determined by the ability of its condensation product with β-naphthol, N-(3-ethyl-2,5-dimethylphenyl)-β-naphthylamine (XVI), to yield a benzo[*a*]phenarsazine derivative (XVII) with arsenic trichloride. This reaction provided the proof for the presence of a free position *ortho* to the amino group (5), thereby eliminating the possibility that the starting amine might be 6-ethyl-2,5-dimethylaniline.

The fact that 3,4-dimethylacetophenone is preferentially nitrated at position 6 showed the importance of the *para*-orienting effect of methyl radicals, an effect which can supersede even the *meta*-directing influence of the keto group. It should be mentioned in this respect that Claus (6) showed that the nitration of 2,4-dimethylacetophenone (XVIII) yielded mostly the 5-nitro derivative (XIX) and only a little of the 3-isomer (XX).



EXPERIMENTAL

Preparation of intermediates. 3,4- and *2,5-Dimethylacetophenone* were prepared from *ortho-* and *para*-xylene with acetyl chloride and aluminum chloride in the usual way (7). *3,4-Dimethylacetanilide* was best synthesized from the oxime of 3,4-dimethylacetophenone by a Beckmann rearrangement with phosphorus pentachloride in ether.

3,4-Dimethyl-6-nitroacetophenone (II). To a solution of 74 g. of 3,4-dimethylacetophenone in 150 ml. of concentrated sulfuric acid cooled at −5°, a mixture of 40 ml. of nitric acid (d^{15} 1.41) with 60 ml. of sulfuric acid was added dropwise with stirring, the temperature being maintained below 0°. At the end of the reaction, the nitro derivative (II) began to crystallize; the solid obtained on pouring into ice water gave on recrystallization from aqueous methanol pale yellow prisms, m.p. 120°. (yield, 75%).

Anal. Calc'd for $C_{10}H_{11}NO_3$: N, 7.3. Found: N, 7.5.

6-Amino-3,4-dimethylacetophenone (V). (a) The foregoing nitro derivative (18 g.) suspended in 120 ml. of concentrated hydrochloric acid was reduced by 119 g. of stannous chloride; the amine obtained in 90% yield on basification boiled at 164°/13 mm. and crystallized from aqueous methanol as pale yellow leaflets, m.p. 131°.

Anal. Calc'd for $C_{10}H_{13}NO$: C, 73.6; H, 8.0.

Found: C, 73.4; H, 8.2.

(b) A mixture of 100 g. of 3,4-dimethylacetanilide, 87 g. of acetyl chloride, and 315 g. of aluminum chloride in carbon disulfide was refluxed on a water-bath for 1½ hours. The solvent was decanted, and the residue treated with dilute hydrochloric acid. The

crude N-acetylated amino ketone obtained was hydrolyzed with boiling hydrochloric acid, and after basification the free amine was vacuum-distilled. Yield, 52 g.

A cooled solution of 6.5 g. of this substance in 25 ml. of concentrated hydrochloric acid (*d.* 1.19) was diazotized with 2.9 g. of sodium nitrite in 12 ml. of water, and the solution obtained was treated with 40 ml. of a 50% aqueous solution of hypophosphorous acid. The mixture was kept overnight at 0°, and the 3,4-dimethylacetophenone obtained was steam-distilled (yield, 3.5 g.). On oxidation with aqueous sodium hypobromite, it gave *3,4-dimethylbenzoic acid* (8), melting at 165° after recrystallization from benzene.

6-Ethyl-3,4-dimethylaniline (VIII). A solution of 30 g. of the amino ketone (V), 30 g. of 90% hydrazine hydrate, and 30 g. of potassium hydroxide in diethylene glycol was slowly heated up to boiling point and refluxed for four hours. After dilution with water, the amine obtained in 80% yield was steam-distilled; it formed a pale yellow oil, boiling at 243°, n_D^{24} 1.5480.

Anal. Calc'd for $C_{10}H_{15}N$: C, 80.5; H, 10.1.
Found: C, 80.3; H, 10.2.

The N-acetyl derivative, prepared with acetyl chloride in benzene, crystallized from aqueous methanol as colorless needles, m.p. 161°.

Anal. Calc'd for $C_{12}H_{17}NO$: N, 7.3. Found: N, 7.2.

A by-product of the reduction of (V) was its *azine*, crystallizing from ethanol in shiny yellow leaflets, m.p. 285°.

Anal. Calc'd for $C_{20}H_{26}N_4$: N, 17.4. Found: N, 17.1.

Nitration of 2,5-dimethylacetophenone. This ketone (37 g.), nitrated at −5° in the usual way with 20 ml. of nitric acid, gave an 80% yield of a solid mixture of nitro derivatives which was directly reduced with 190 g. of stannous chloride in 200 ml. of hydrochloric acid. After the usual treatment, the mixture of the amino ketones obtained was vacuum-fractionated.

4-Amino-2,5-dimethylacetophenone (XII). The higher-boiling portion (198°/16 mm.) crystallized from methanol as long colorless needles, m.p. 157°; the literature (3) gives m.p. 156°. The Kishner-Wolff-Huang-Minlon reduction yielded 4-ethyl-2,5-dimethylaniline, b.p. 244°, whose N-acetyl derivative had m.p. 144°; the literature (3, 4) gives m.p. 144°.

3-Amino-2,5-dimethylacetophenone (XIII). This compound was obtained in 35% yield as a yellow viscous oil, boiling at 158°/12 mm., n_D^{18} 1.5755.

Anal. Calc'd for $C_{10}H_{13}NO$: N, 8.6. Found: N, 8.5.

3-Ethyl-2,5-dimethylaniline (XV). Reduction of 20 g. of the foregoing compound yielded 12 g. of an amine, boiling at 240–241°, n_D^{24} 1.5500.

Anal. Calc'd for $C_{10}H_{15}N$: C, 80.5; H, 10.1.
Found: C, 80.6; H, 10.0.

This amine was characterized by an *N-acetyl derivative* which crystallized from aqueous methanol as long colorless needles, m.p. 130°.

Anal. Calc'd for $C_{12}H_{17}NO$: N, 7.3. Found: N, 7.3.

12-Chloro-9-ethyl-8,11-dimethyl-7,12-dihydrobenzo[α]phenarsazine (XVII). A mixture of 3 g. of 3-ethyl-2,5-dimethylaniline, 7.5 g. of β-naphthol, and 0.1 g. of iodine was heated for 12 hours at 190–200°. The reaction product was taken up in benzene, washed with an aqueous solution of sodium hydroxide, and dried over sodium sulfate; the residue after evaporation of benzene yielded on distillation 4 g. of *N-(3-ethyl-2,5-dimethylphenyl)-β-naphthylamine* (XVI), boiling at 255°/15 mm., which readily solidified on trituration with ligroin. A solution of 2 g. of this amine and 1.6 g. of arsenic trichloride in 15 ml. of *o*-dichlorobenzene was refluxed for one hour; after cooling, the solid obtained was collected and recrystallized from chlorobenzene; yield, 1.8 g. of shiny orange-yellow needles, m.p. 253° (decomp. above 220°).

Anal. Calc'd for $C_{20}H_{19}AsClN$: C, 62.6; H, 5.0.
Found: C, 62.4; H, 5.2.

SUMMARY

1. The nitration of 3,4-dimethylacetophenone has been shown to give mostly the 6-nitro derivative together with a little of the 5-isomer; in the case of 2,5-

dimethylacetophenone, a mixture of the 3- and 4-nitro derivatives was obtained.

2. These nitroketones were reduced to the corresponding amino ketones, and the latter were further reduced to substituted ethylxylidines of known constitution.

PARIS V^e, FRANCE

REFERENCES

(1) BUU-HOÏ, ECKERT, AND ROYER, *Compt. rend.*, **232**, 1356 (1951).
(2) EMMERLING AND ENGLER, *Ber.*, **3**, 886 (1870); CAMPS, *Arch. Pharm.*, **240**, 5 (1902); RUPE, BRAUN, AND VON ZEMBRZUSKI, *Ber.*, **34**, 3522 (1901).
(3) ECKERT, ROYER, AND BUU-HOÏ, *Compt. rend.*, **233**, 1461 (1951).
(4) HODGKINSON AND LIMPACH, *J. Chem. Soc.*, **61**, 421 (1892).
(5) See BUU-HOÏ AND ROYER, *J. Chem. Soc.*, 795 (1951).
(6) CLAUS, *J. prakt. Chem.*, [2] **41**, 493 (1890).
(7) CLAUS AND WOLLNER, *Ber.*, **18**, 1856 (1885); CLAUS, *J. prakt. Chem.*, [2] **41**, 409 (1890).
(8) LELL AND BENZ, *Ber.*, **24**, 2115 (1891).